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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

SRI

Office Action Summary	Application No.	Applicant(s)	
	09/778,388	SZOKA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,5-7 and 10-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,5-7 and 10-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 2/25/04.

Claims 1, 2, 5-7, 10-52 remain pending and under consideration in this Office Action.

Rejections Withdrawn

The rejection of claims 1, 2, and 10 under 35 USC 102 over Klaveness is withdrawn in view of Applicant's amendment.

The rejection of claims 1 and 5 under 35 USC 103 over Klaveness is withdrawn in view of Applicant's amendment.

Drawings

Applicant filed informal drawings on 2/7/01 that are acceptable for the purposes of examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, and 10-14 and 16are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, and 10-14 are indefinite because it is unclear what is intended by "A composition comprising a hydrophilic portion and a hydrophobic

portion joined by an ortho ester linker having an amphipathic characteristic". In particular it is unclear whether the phrase "amphipathic characteristic" is meant to describe the nature of the composition as a whole, or the is meant to describe the nature of the ortho ester linker. As such, one of skill in the art cannot know the metes and bounds of the genus of ortho ester linkers embraced by the claims.

Claim 16 is indefinite because it is unclear what are the metes and bunds of a "dichloromethylmethyl ether derivative". The specification provides no limiting definition and it is unclear to what extent atoms can be added to, subtracted from, or substituted in dichloromethylmethyl ether and result in what Applicant considers a "derivative".

Response to Arguments

Applicant's arguments filed 2/25/04 have been fully considered but they are not persuasive.

Applicant addresses the rejection at page 10 of the response. Applicant argues that one of skill in the art would readily recognize that such derivatives must share the basic chemical nature of the named compound, but could have simple substitutions that do not fundamentally alter the characteristics of the compound. This argument is unpersuasive because it is only a statement of opinion, and lacks any support, evidentiary or otherwise.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-7, and 10-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5, and 10-14 were amended to recite by "A composition comprising a hydrophilic portion and a hydrophobic portion joined by an ortho ester linker having an amphipathic characteristic". To the extent that this phrase is interpreted to require an ortho ester linker with an amphipathic characteristic, it represents new matter because the specification does not disclose or contemplate an ortho ester linker that, in and of itself, has an amphipathic characteristic. The specification discloses only ortho ester and diorthoester linkers that lack sufficient hydrophobic character to be considered amphipathic. It is apparent from page 13, lines 1-5 of Applicant's response filed 2/25/04, that Applicant intended the phrase "amphipathic characteristic" to refer to the composition as a whole. However, the claim as written is ambiguous at best, and the Examiner must consider all reasonable interpretations. In this case, the interpretation described above comprises new matter. This rejection could be overcome by rewriting the preamble as "An amphipathic molecule comprising a hydrophilic portion and a hydrophobic portion joined by an ortho ester linker".

The body of the claim could be amended to require that hydrolysis of the ortho ester linker directly results in cleavage of the molecule and separation of the hydrophobic and hydrophilic portions.

Independent claims 19, 30, 38, 42, 48, and 50, have been amended in a way that introduces new matter into the disclosure. Previously these claims required that a hydrophobic portion of an amphipathic compound must attach directly to an ortho ester through an oxygen atom, and that cleavage of the ortho ester must result directly in detachment of the hydrophilic and hydrophobic portions of the amphipathic compound. This combination of limitations was supported in the specification as filed, see e.g. Figures 1 and 2. However, the claims have been amended to broaden their scope to embrace amphipathic ortho ester compounds wherein cleavage of the ortho ester must result directly in detachment of the hydrophilic and hydrophobic portions of the amphipathic compound, and wherein the hydrophobic portion need not be attached to the ortho ester through an oxygen. Applicant has not pointed to any support in the specification for this genus, and none is apparent. As such, the claims recite new matter. Note that claims were previously rejected for requiring direct detachment of hydrophobic and hydrophilic moieties upon ortho ester hydrolysis (Office Action of 3/12/03), and this rejection was overcome by addition of the limitation requiring attachment of the hydrophobic moiety to the ortho ester through an oxygen atom (amendment of 7/16/03).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42, and 50-52 stand rejected under 35 U.S.C. 102(e) as being anticipated by Nantz (US Patent 6,200,599, issued 3/15/01).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic head group comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the aggregate. See e.g. column 2, line 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See

column 9, lines 24-31. Nantz also teaches that the lipid may be prepared as a powder prior to rehydration and administration. See e.g. column 20, lines 44-56, and column 23, lines 7-15.

Claims 16, 30, 31, 34, and 35 are included in this rejection because the composition of Nantz appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Arguments

Applicant's arguments filed 2/25/04 have been fully considered but they are not persuasive.

Applicant addresses the rejection at pages 11 and 12 of the response. Applicant's arguments concern a portion of Nantz not relied upon in the rejection.

Applicant's arguments are based on the structures in Fig.1, and the hydrolysis mechanism in Fig.2, of Nantz. In contrast, the rejection relies upon the structure disclosed at column 2, line 44 to column 3, line 18, wherein A and A1 are both O, and R2 is an alkoxy group. This structure is analogous to those disclosed in instant Fig.2, wherein R1, R2, (CH2)x, and (CH2)y of Nantz are analogous to R4, R1, R3 and R2, respectively, from instant Fig. 2. Guo et al (2001, of record) taught that, under acidic conditions, this structure would hydrolyze to separately release each of instant R1-R4. See scheme 1 on page 292, column 1 of Guo. This allows separation of a hydrophilic from hydrophobic groups directly as a result of hydrolysis. Applicant has not provided any evidence or reasoning to indicate that the structures relied upon in the rejection are not analogous to those claimed and would not behave in a similar manner under acid hydrolysis conditions. As such, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42, 50-52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al

(US patent 5,395,619, issued 3/7/95) in view of Nantz (US Patent 6,200,599, issued 3/15/01), and Unger et al (US Patent 6,028,066, issued 2/22/00).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68. The polymers may comprise a targeting ligand. See column 10, lines 39-52.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an ortho ester; the particular hydrophobic groups distearoylglycerol, dimyristoylglycerol, dipalmitoylglycerol, cholesterol, ceramides, phosphatidylcholine, phosphatidylserine, phosphatidylglycerol, cholesterol sulfate, DOTAP, or DOTMA; or the particular targeting ligands hyaluronan, peptides, receptor antagonists, carbohydrates, protein hormones or cytokines attached to the hydrophilic polymer.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic molecule comprising an acid labile ortho ester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract, column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be

oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Unger teaches that distearoylglycerol, dimyristoylglycerol, dipalmitoylglycerol, cholesterol, ceramides, phosphatidylcholine, phosphatidylserine, phosphatidylglycerol, cholesterol sulfate, DOTAP, and DOTMA are lipids that useful in the formation of liposomes. See e.g. column 23, line 35 to 53, column 24, lines 2 and 3, and column 29, lines 49-52. Unger teaches that lipid vesicles can be stabilized by including hydrophilic polymers such as polyethylene glycol or polyvinylpyrrolidone. The polymer may have a molecular weight from about 400 to about 100,000. Unger exemplifies distearoylphosphatidyl ethanolamine PEG 5000. The polymer-conjugated lipid may be present in the vesicle at from 8-15% of the total lipid. See column 39, lines 15-60. Unger also teaches a variety of targeting ligands including hyaluronan, peptides, receptor antagonists, carbohydrates, protein hormones and cytokines that can be attached to the lipid via the hydrophilic polymer. See column 48, lines 11-16, 20-22, 39-42, and 62-65.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from endosomes as taught by Nantz. It would have been obvious to use any of the hydrophobic or targeting groups taught by Unger. MPEP

2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Unger are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes. Similarly the targeting ligands are art-recognized equivalents inasmuch as it recognized that they can be attached to lipids via hydrophilic polymers.

Claim 22 is included in this rejection because the lipid composition of the liposomes is recognized as a variable that is optimized by those of ordinary skill in the art. For example, Unger teaches a variety of proportions of lipid components, including a PEG5000- modified distearoyl-glycerolipid lipid from 8-15% of the total lipid of a vesicle. It would have been obvious to use methoxypolyethylene glycol 2000 diorthoester-distearoyl glycerol in an amount from 3-15% of the total lipid because: Applicant admitted on the record in Paper No. 5, page 1, that methoxypolyethylene glycol is an art recognized equivalent of PEG; Unger teaches that a range of PEGs overlapping the recited "2000" may

function in the invention, and that glycerol distearate is a lipid that is useful for formation of liposomes; Zalipsky teaches that any lipid useful for forming liposomes may be modified with a hydrophilic polymer such as PEG; and Nantz teaches the improvement of using an ortho ester linker to improve DNA delivery. Note that each of the hydrophilic polymers of Zalipsky has a terminal hydroxyl that could server in formation of the alkoxy group of Nantz, meeting the limitation of instant claim 19 requiring ortho ester attachment through an oxygen atom.

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Huang et al (US Patent 6,008,202 issued 12/28/99).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic head group comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic

polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach liposome compositions comprising the lipids phosphatidic acid, DDAB, or cholesteryl hemisuccinate.

Huang teaches that phosphatidic acid, DDAB, or cholesteryl hemisuccinate are lipids that useful in the formation of liposomes. See e.g. column 10, line 56, and column 12, lines 14-21. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view Sankaram et al (US Patent 5,993,850 issued 11/30/99).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a

hydrophilic head group comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach liposome compositions comprising cardiolipid or squalene.

Sankaram teaches cardiolipin and squalene are useful in the formation of liposomes. See e.g. column 7, lines 47-57. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also

Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view Sprott et al (US Patent 6,132,789, issued 10/17/00).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic head group comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach compositions comprising coenzyme Q.

Sprott teaches that coenzyme Q when incorporated into liposomes increases the delivery of associated compounds. See e.g. column 4, lines 32-44,

thus one would have been motivated to include it in the liposomal compositions of Nantz.

Claims 1, 2, 5, and 6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al (US patent 5,395,619, issued 3/7/95) in view of Nantz (US Patent 6,200,599, issued 3/15/01), and Haynes et al (US Patent 5,015,483 issued 5/14/91).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an ortho ester, or the hydrophobic groups tocopherol, ceramides, or cholesterol.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic molecule comprising an acid labile ortho ester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract.

Haynes teaches that lipids that can be incorporated into liposomes include tocopherol, ceramides, and cholesterol. See column 10, lines 4-13, and column 14, lines 3-23.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from endosomes. It would have been obvious to use any of the hydrophobic groups taught by Haynes. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Haynes are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 2, 5, and 6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al (US patent 5,395,619, issued 3/7/95) in view of

Nantz (US Patent 6,200,599, issued 3/15/01), and Sprott et al (US Patent 6,132,789, issued 10/17/00).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an ortho ester, or the hydrophobic group coenzyme Q.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic molecule comprising an acid labile ortho ester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract.

Sprott teaches that coenzyme Q is a lipid that can be that can be incorporated into liposomes, and which can promote phagocytosis of the liposomes. See e.g. column 3, lines 27-46.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from endosomes. It would have been obvious to use any of the

hydrophobic groups taught by Sprott, including coenzyme Q. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Sprott are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes.

Thus the invention as a whole was *prima facie* obvious.

Claims 38 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Eppstein et al (US Patent 4,897,355, issued 1/30/90).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic head group comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the . See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note

that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach administration of the lipid formulations as a dry powder.

Eppstein teaches that lipid formulations may be prepared and administered as powders. See column 13, lines 18-20.

It would have been obvious to administer the composition of Nantz as a powder because, in view of the teachings of Eppstein, it was routine in the art at the time of the invention to do so.

Thus the invention as a whole was *prima facie* obvious.

Claims 38, 40 and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Eppstein et al (US Patent 4,897,355, issued 1/30/90) and Lishko et al (US Patent 5,753,263, issued 5/19/98).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic head group comprising an ammonium ion, and methods of delivering

the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the ortho ester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach rehydration of a drug-containing dry powder liposome formulation prior to administration.

Eppstein teaches that lipid formulations may be prepared and administered as powders. See column 13, lines 18-20.

Lishko teaches lyophilization of liposome compositions for storage, followed by rehydration.

It would have been obvious to one of ordinary skill in the art at the time of the invention to lyophilize the compositions of Nantz in order to store them, and to rehydrate them prior to use. One would have been motivated to do so because one of ordinary skill in the art appreciates that it is efficient to make large quantities of a composition which can be conveniently stored and used when needed. Given the teachings of Lishko one of ordinary skill in the art could have lyophilized and rehydrated the compositions of Nantz with a reasonable

expectation of success. The decision to do so is design choice made by one of ordinary skill in the art

Thus the invention as a whole was *prima facie* obvious.

Claims 42 and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Needham, US Patent 5,827,533 (issued 10/27/98).

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42, column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that in Formula I at column 2, A and A1 may be oxygen, R2 may be an alkoxy group, and (CH2)x and (CH2)y attach to the ortho ester a hydrophilic head group (ZQR4). As a result, the structure of Nantz is analogous to the structure set forth by applicant in instant Fig. 2. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach a method of combining an encapsulator suspension with a dry film of a lipidic ortho ester composition.

Needham teaches a method of encapsulating micelles in lipid vesicles wherein lipids were dried to a film and rehydrated with a suspension of micelles containing an active agent.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Needham by using the lipids of Nantz in either or both of the micelle and the vesicle. One would have been motivated to do so in order to improve intracellular release of the active agent upon entry into the endosomal pathway.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 2/25/04 have been fully considered but they are not persuasive.

Applicant addresses the rejections at pages 13-16 of the response. As in the response to the 102 rejection, Applicant's arguments concern a portion of Nantz not relied upon in these 103 rejections. Applicant's arguments are based on the structures in Fig.1, and the hydrolysis mechanism in Fig.2, of Nantz. In contrast, the rejection relies upon the structure disclosed at column 2, line 44 to column 3, line 18, wherein A and A1 are both O, and R2 is an alkoxy group. This structure is analogous to those disclosed in instant Fig.2, wherein R1, R2, (CH2)x, and (CH2)y of Nantz are analogous to R4, R1, R3 and R2, respectively, from instant Fig. 2. Guo et al (2001, of record) taught that, under acidic conditions, this structure would hydrolyze to separately release each of instant R1-R4. See scheme 1 on page 292, column 1 of Guo. This allows separation of a hydrophilic from hydrophobic groups directly as a result of hydrolysis. Applicant has not provided any evidence or reasoning to indicate that the

structures relied upon in the rejection are not analogous to those claimed and would not behave in a similar manner under acid hydrolysis conditions. As such, the rejections are maintained.

Conclusion

No claim is allowed.

Claims 11-14, 17, 18, 23, 33, 37, 43, 44, and 46-49 are free of the art of record.

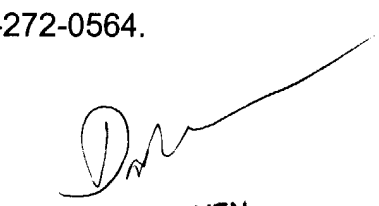
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone

number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.



Richard Schnizer, Ph.D.